IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty. Docket: KATSUKI2

In re Application of:	) Conf. No.: 8366
Hisakazu KATSUKI et al.	) Art Unit: 1616
Appln. No.: 10/588,609	) Examiner: S. N. Qazi
Filed: August 7, 2006	) Washington, D.C.
For: ED-71 PREPARATION	)

DECLARATION UNDER 37 CFR 1.132

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22314

Sir:

I, Hisakazu Katsuki, a Japanese citizen, hereby declare as follows:

1. I received a master's degree in Pharmaceutical Science (Clinical pharmacy course) in March 1995, at Kumamoto University, Kumamoto-shi, Japan.

2. I have been employed by Chugai Pharmaceutical Co. Ltd., the Assignee of this application, since 1995, and I have worked as a researcher for the Ukima Research Laboratories of the Assignee, at Kita-ku, Tokyo, Japan.

3. I have read the Official Action issued against the subject patent application mailed on March 20, 2009 and have noted the Examiner's allegation that Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable

over CHEN et al. (WO 03/047595), MIYAMOTO et al. (US Patent 4,666,634) and Chem. Pharm. Bull. (all 892 references).

4. I, one of inventors of the subject application, conducted the following experiment, in order to evidence that the method of Claims 12 and 13 achieves results greater than those which would have been expected from the combination of the prior arts.

5. The results are true and correct to the best of my knowledge.

Method:

To compare antioxidants, BHA, catechin, tocopherol, ferulic acid, BHT, citric acid, and thiolactic acid, with one another with respect to effectiveness in suppressing generation of (5E,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol (hereinafter referred to as "trans form of ED-71") in an oily preparation containing (5Z,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol (hereinafter referred to as "ED-71"), soft capsules filled with a solution of ED-71 and one of the antioxidants in a medium-chain triglyceride, caprylic/capric triglyceride (commercially available as "MCT(ODO-C)"), were prepared and stored under conditions for accelerated degradation of ED-71. After the storage, the capsules were each analyzed for the amount of trans form of ED-71 formed during the storage.

1) Preparation of soft capsules

ED-71 and one of the antioxidants were dissolved in caprylic/capric triglyceride to prepare a solution containing 1 μg (2 nmol) of ED-71 and 11.9 nmol of the antioxidant per 100 mg of the solution. Then, 100 mg of the solution was injected into an empty soft capsule, the shell of which is composed of 54.71 mg of gelatin, 8.34 mg of D-sorbitol and 1.95 mg of caramel, by means of a syringe with a needle. The capsule was sealed with gelatin.

These procedures were repeated for each of the antioxidants to provide sealed soft capsules containing various types of antioxidant.

2) Storage

The sealed soft capsules were placed into a bottle which was then sealed. The bottle was stored at 40°C for two months.

3) Determination of trans form of ED-71

After completion of storage, the sealed soft capsules were removed from the bottle, and the solutions were extracted from the capsules, and 50-μL aliquots thereof were then subjected to HPLC analysis to determine the amount of trans form of ED-71 formed during the storage.

Column: YMC-Pack ODS AM-303 (250 × 4.6 mm, 5 μm)

Mobile phase: acetonitrile/water =1:1

Flow rate: 1.2 mL/min

Peak detection: 265 nm

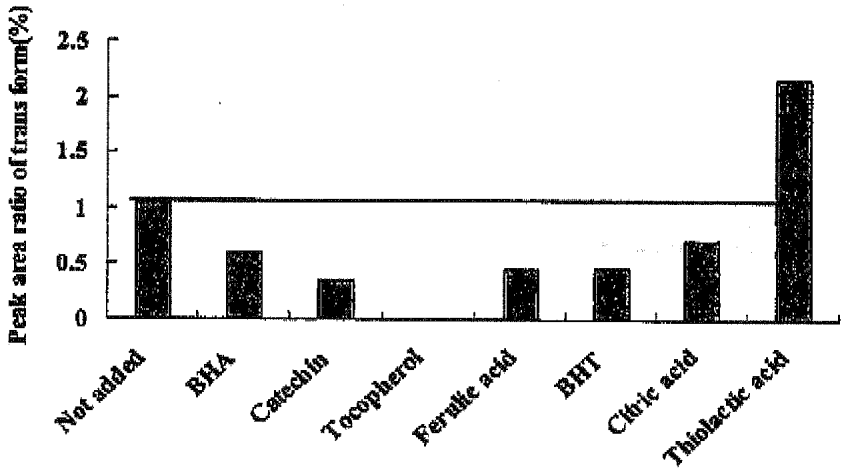
Column temperature: 30°C

Running time: 35 min

A peak area ratio of trans form of ED-71 relative to the total sum of detected peak areas was calculated and used as an index of the amount of trans form of ED-71.

Results:

The figure shown below is a graphical presentation of the results obtained. The lower the level of the bar in the figure, the greater the effectiveness of the antioxidant designated immediately below the bar in suppressing the formation of trans form of ED-71.



As can be seen form the figure, a dramatic effect on the suppression of the formation of trans form of ED-71 is observed when tocopherol is added. Tocopherol is far more effective than the other antioxidants tested, i.e., BHA, catechin, ferulic acid, BHT, citric acid and thiolactic acid.

The results indicate that the effect of the inventive method currently claimed in Claims 12 and 13 where antioxidants are limited to dl-α-tocopherol is greater than that which would have been expected from a combination of the prior arts, and that the effect is of a significant, practical advantage. Such an effect would not have been expected from the disclosures of the prior arts.

Therefore, the currently claimed method is unobvious over the prior arts.

I hereby further declare that all statements made herein are to my own knowledge and belief true, and that all statements made on information and belief are believed to be true, and that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

August 20, 2009 Hisakazu Katsuki

Hisakazu Katsuki